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Correlative Neuroanatomy

twenty-third edition

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The Autonomic Nervous System

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The autonomic (visceral) nervous system (ANS) is concerned with control of the target tissues: the cardiac muscle, the smooth muscle in viscera, and the glands. It also helps maintain a constant internal body environment (homeostasis). The autonomic nervous system consists of efferent pathways, afferent pathways, and groups of neurons in the brain and spinal cord that regulate the system's functions. Autonomic reflex activity in the spinal cord accounts for some important aspects of autonomic regulation and homeostasis, but it is modulated by supraspinal centers such as brain stem nuclei and the hypothalamus, so that there is a hierarchical organization within the central nervous system itself.

The autonomic nervous system is divided into two anatomically distinct divisions which have largely opposing actions: the **sympathetic (thoracolumbar)** and **parasympathetic (craniosacral)** divisions (Fig 20-1).

AUTONOMIC OUTFLOW

The efferent components of the autonomic system are the sympathetic and parasympathetic divisions, which arise from preganglionic cell bodies in different locations. The autonomic outflow system is organized more diffusely than the somatic motor system. In the somatic motor system, lower motor neurons project directly from the spinal cord or brain, without an interposed synapse, to innervate a relatively small group of target cells (somatic muscle cells). In contrast, a more slowly conducting two-neuron chain characterizes the autonomic outflow. The cell body of the primary neuron (the **presynaptic**, or **preganglionic**, neuron) within the central nervous system is located in the intermediolateral gray column of the spinal cord or in the brain stem nuclei (see Chapter 8). It sends its axon, which is usually a small-diameter, myelinated B fiber (see Chapter 3), out to synapse with the secondary neuron (the **postsynaptic**, or **postganglionic**, neuron) located in one of the autonomic ganglia. From there, the postganglionic axon passes to its terminal distribution in

a target organ. Most postganglionic autonomic axons are unmyelinated C fibers.

The autonomic outflow system projects widely to most target tissues and is not as highly focused as the somatic motor system. Since the postganglionic fibers outnumber the preganglionic neurons by a ratio of about 32:1, a single preganglionic neuron may control the autonomic functions of a rather extensive terminal area.

Sympathetic Division

The sympathetic (**thoracolumbar**) division of the autonomic nervous system arises from preganglionic cell bodies located in the intermediolateral cell columns of the 12 thoracic segments and the upper two lumbar segments of the spinal cord (Fig 20-2).

A. Preganglionic Sympathetic Efferent Fiber System: Preganglionic fibers are mostly myelinated. Coursing with the ventral roots, they form the **white communicating rami** of the thoracic and lumbar nerves, through which they reach the ganglia of the sympathetic chains or trunks (Fig 20-3). These **trunk ganglia** lie on the lateral sides of the bodies of the thoracic and lumbar vertebrae. Upon entering the ganglia, the fibers may synapse with a number of ganglion cells, pass up or down the sympathetic trunk to synapse with ganglion cells at a higher or lower level, or pass through the trunk ganglia and out to one of the collateral (intermediary) sympathetic ganglia (eg, the **celiac** and **mesenteric ganglia**).

The **splanchnic nerves** arising from the lower seven thoracic segments pass through the trunk ganglia to the **celiac** and **superior mesenteric ganglia**. There, synaptic connections occur with ganglion cells whose postganglionic axons then pass to the abdominal viscera via the **celiac plexus**. The splanchnic nerves arising from spinal cord segments in the lowest thoracic and upper lumbar region convey fibers to synaptic stations in the **inferior mesenteric ganglion** and to small ganglia associated with the **hypogastric plexus** through which postsynaptic fibers are distributed to the lower abdominal and pelvic viscera.

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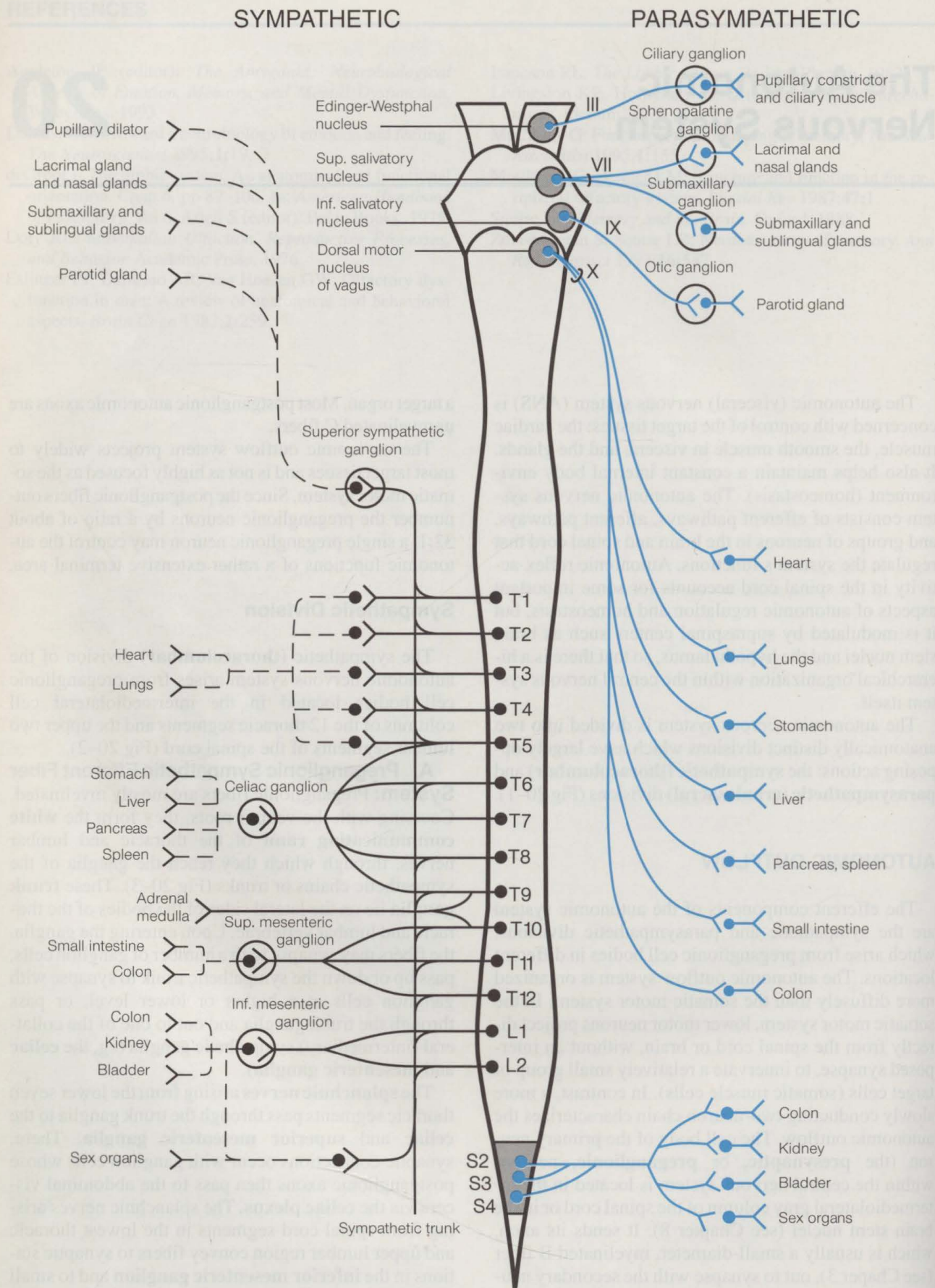


Figure 20-1. Overview of the sympathetic nervous system, and of its sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions.

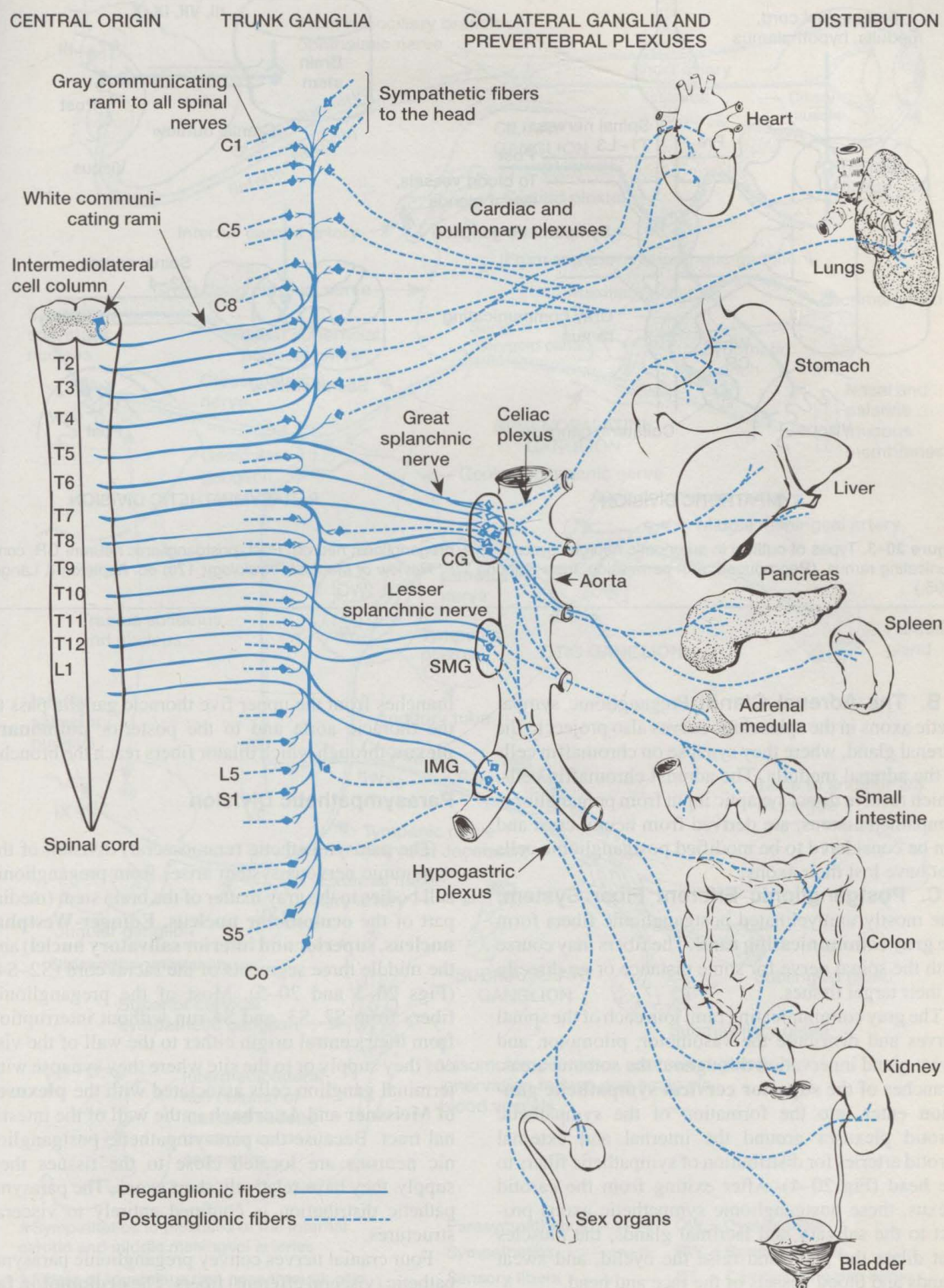


Figure 20-2. Sympathetic division of the autonomic nervous system (left half). CG, celiac ganglion; SMG, superior mesenteric ganglion; IMG, inferior mesenteric ganglion.

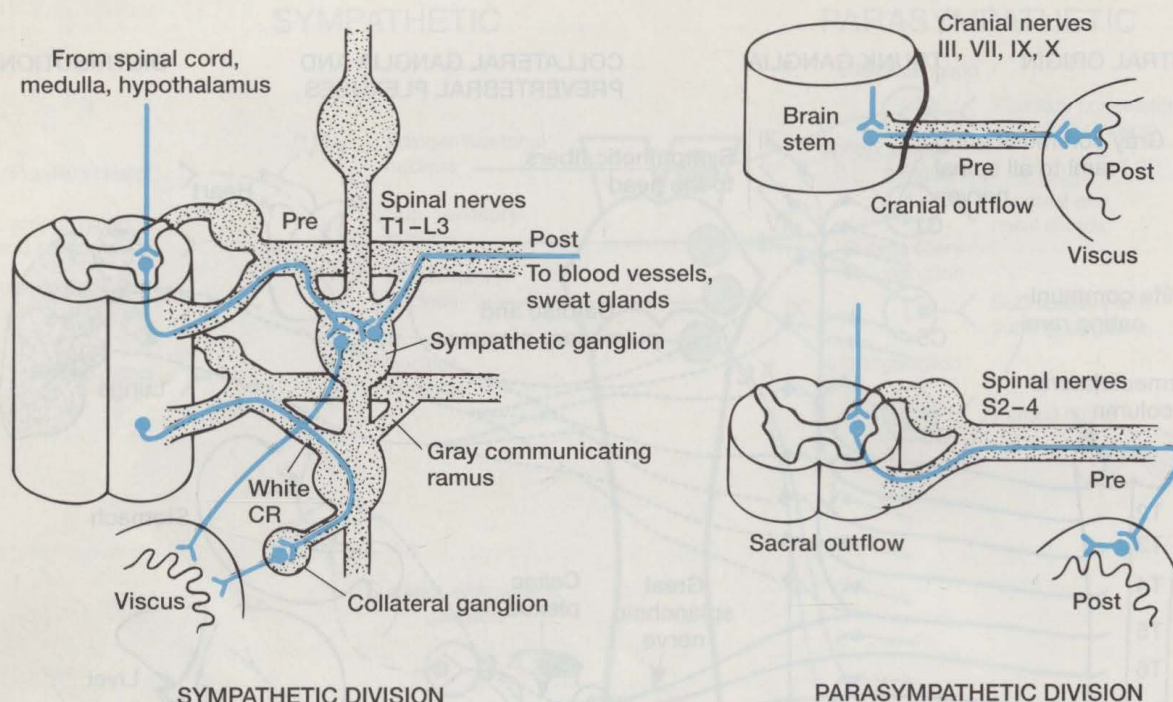


Figure 20-3. Types of outflow in autonomic nervous system. Pre, preganglionic neuron. Post, postganglionic neuron. CR, communicating ramus. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.)

B. The Adrenal Gland: Preganglionic sympathetic axons in the splanchnic nerves also project to the adrenal gland, where they synapse on chromaffin cells in the adrenal medulla. The adrenal chromaffin cells, which receive direct synaptic input from preganglionic sympathetic axons, are derived from neural crest and can be considered to be modified postganglionic cells that have lost their axons.

C. Postganglionic Efferent Fiber System: The mostly unmyelinated postganglionic fibers form the **gray communicating rami**. The fibers may course with the spinal nerve for some distance or go directly to their target tissues.

The gray communicating rami join each of the spinal nerves and distribute the vasomotor, pilomotor, and sweat gland innervation throughout the somatic areas. Branches of the **superior cervical sympathetic ganglion** enter into the formation of the sympathetic carotid plexuses around the internal and external carotid arteries for distribution of sympathetic fibers to the head (Fig 20-4). After exiting from the carotid plexus, these postganglionic sympathetic axons project to the salivary and lacrimal glands, the muscles that dilate the pupil and raise the eyelid, and sweat glands and blood vessels of the face and head.

The superior **cardiac nerves** from the three pairs of cervical sympathetic ganglia pass to the **cardiac plexus** at the base of the heart and distribute cardio-accelerator fibers to the myocardium. Vasomotor

branches from the upper five thoracic ganglia pass to the thoracic aorta and to the posterior **pulmonary plexus**, through which dilator fibers reach the bronchi.

Parasympathetic Division

The parasympathetic (craniosacral) division of the autonomic nervous system arises from preganglionic cell bodies in the gray matter of the brain stem (medial part of the **oculomotor nucleus**, **Edinger-Westphal nucleus**, **superior and inferior salivatory nuclei**) and the middle three segments of the sacral cord (S2–S4) (Figs 20-3 and 20-5). Most of the preganglionic fibers from S2, S3, and S4 run without interruption from their central origin either to the wall of the viscus they supply or to the site where they synapse with terminal ganglion cells associated with the **plexuses of Meissner** and **Auerbach** in the wall of the intestinal tract. Because the parasympathetic postganglionic neurons are located close to the tissues they supply, they have relatively short axons. The parasympathetic distribution is confined entirely to visceral structures.

Four cranial nerves convey preganglionic parasympathetic (visceral efferent) fibers. The **oculomotor**, **facial**, and **glossopharyngeal nerves** (cranial nerves III, VII, and IX) distribute parasympathetic or visceral efferent fibers to the head (Fig 20-4; see also Chapters 7 and 8). Parasympathetic axons in these nerves

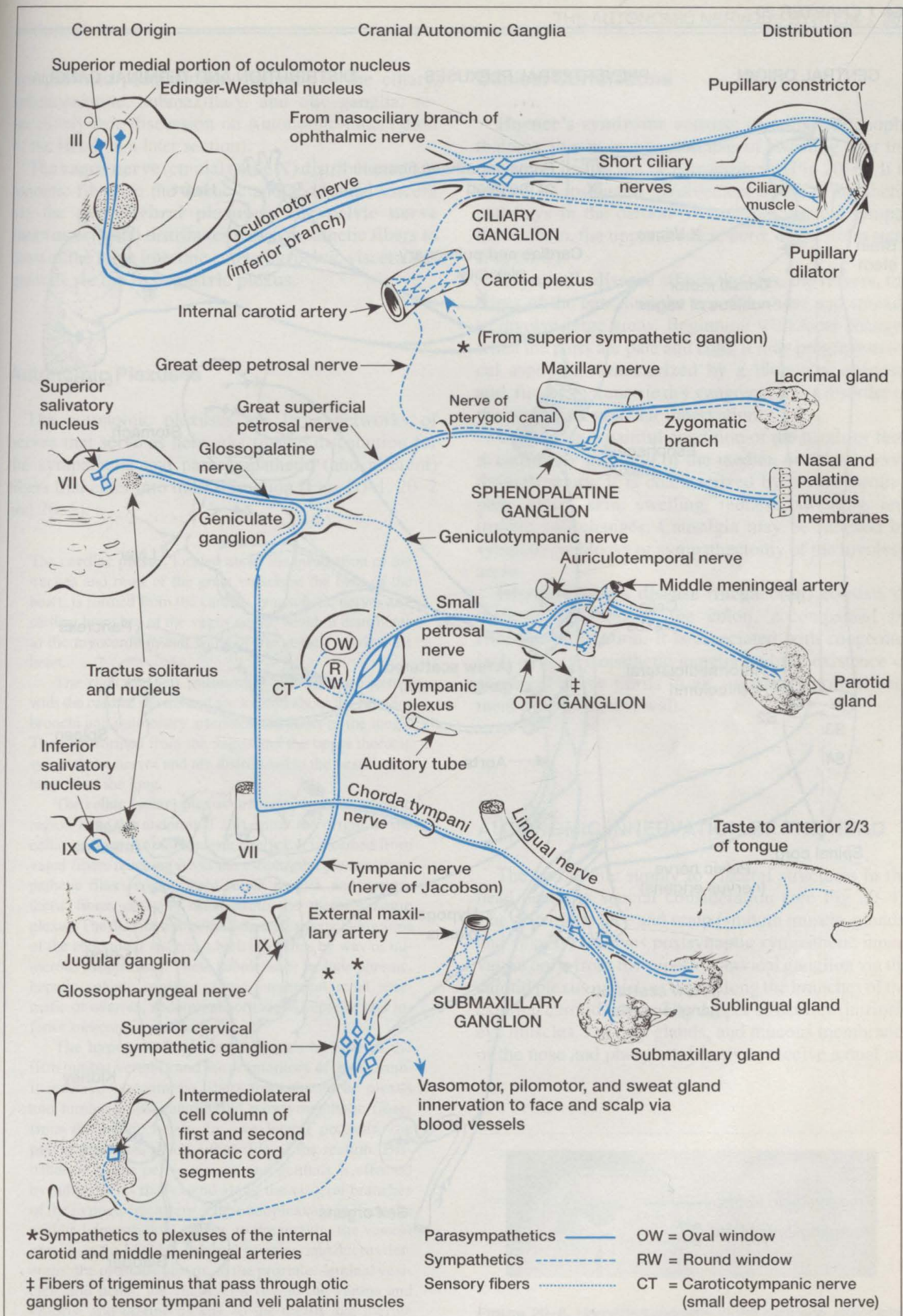


Figure 20-4. Autonomic nerves to the head. OW, oval window; RW, round window; CT, caroticotympanic (small deep petrosal) nerve.

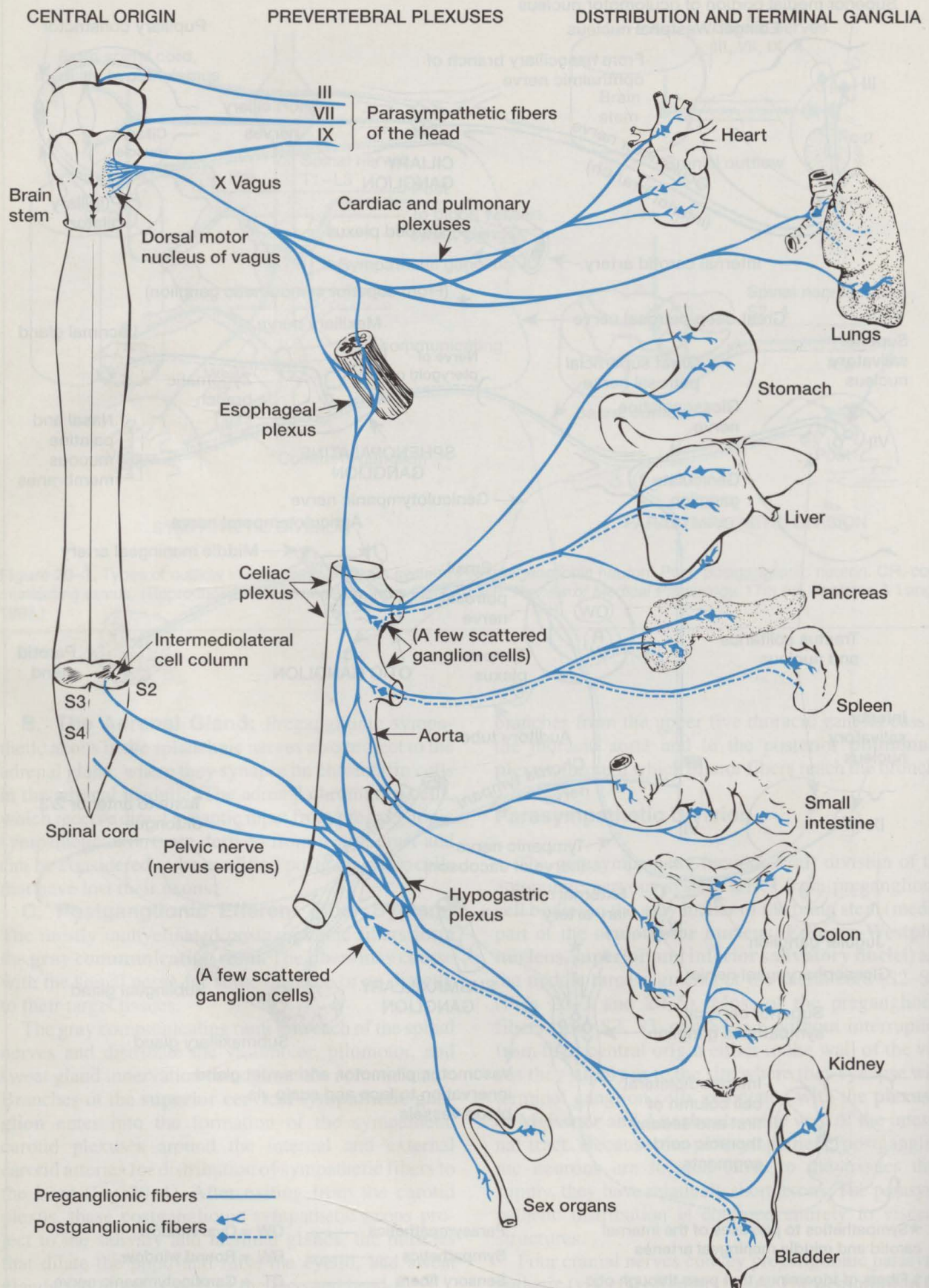


Figure 20-5. Parasympathetic division of the autonomic nervous system (only left half shown).

synapse with postganglionic neurons in the ciliary, sphenopalatine, submaxillary, and otic ganglia, respectively (see discussion on Autonomic Innervation of the Head, in a later section).

The **vagus nerve** (cranial nerve X) distributes its autonomic fibers to the thoracic and abdominal viscera via the **prevertebral plexuses**. The **pelvic nerve** (**nervus erigens**) distributes parasympathetic fibers to most of the large intestine and to the pelvic viscera and genitals via the **hypogastric plexus**.

Autonomic Plexuses

The autonomic plexuses are large networks of nerves that serve as networks for the distribution for the sympathetic and parasympathetic (and afferent) fibers that enter into their formation (Figs 20-1, 20-2 and 20-5).

The **cardiac plexus**, located about the bifurcation of the trachea and roots of the great vessels at the base of the heart, is formed from the cardiac sympathetic nerves and cardiac branches of the vagus nerve, which it distributes to the myocardium and walls of the vessels leaving the heart.

The right and left **pulmonary plexuses** are joined with the cardiac plexus and are located about the primary bronchi and pulmonary arteries at the roots of the lungs. They are formed from the vagus and the upper thoracic sympathetic nerves and are distributed to the vessels and bronchi of the lung.

The **celiac (solar) plexus** is located in the epigastric region over the abdominal aorta near the origin of the celiac and superior mesenteric arteries. It is formed from vagal fibers reaching it via the esophageal plexus, sympathetic fibers arising from celiac ganglia, and sympathetic fibers coursing down from the thoracic aortic plexus. The distribution of the celiac plexus includes most of the abdominal viscera, which it reaches by way of numerous subplexuses. These subplexuses include phrenic, hepatic, splenic, superior gastric, suprarenal, renal, spermatic or ovarian, abdominal aortic, and superior and inferior mesenteric plexuses.

The **hypogastric plexus** is located in front of the fifth lumbar vertebra and the promontory of the sacrum. It receives sympathetic fibers from the aortic plexus and lumbar trunk ganglia and parasympathetic fibers from the pelvic nerve. Its two lateral portions, the **pelvic plexuses**, lie on either side of the rectum. Distribution to the pelvic viscera and genitals is effected by subplexuses that extend along the visceral branches of the hypogastric artery. These subplexuses include the middle hemorrhoidal plexus, to the rectum; the vesical plexus, to the bladder, seminal vesicles, and ductus deferens; the prostatic plexus, to the prostate, seminal vesicles, and penis; the vaginal plexus, to the vagina and clitoris; and uterine plexus, to the uterus and uterine tubes.

Clinical Correlations

Horner's syndrome consists of unilateral enophthalmos, ptosis, miosis, and loss of sweating over the ipsilateral half of the face or forehead (Fig 20-6). It is caused by ipsilateral involvement of the sympathetic pathways in the carotid plexus, the cervical sympathetic chain, the upper thoracic cord, or the brain stem (Fig 20-7).

Raynaud's disease affects the toes, the fingers, the edges of the ears, and the tip of the nose and spreads to involve large areas. Beginning with local changes when the parts are pale and cold, it may progress to local asphyxia characterized by a blue-gray cyanosis and, finally, symmetric dry gangrene. It is a disorder of the peripheral vascular innervation.

Causalgia, a painful condition of the hands or feet, is caused by irritation of the median or sciatic nerve through injury. It is characterized by severe burning pain, glossy skin, swelling, redness, sweating, and trophic nail changes. Causalgia may be relieved by sympathetic blocks or sympathectomy of the involved areas.

Hirschsprung's disease (megacolon) consists of marked dilatation of the colon, accompanied by chronic constipation. It is associated with congenital lack of parasympathetic ganglia and the existence of abnormal nerve fibrils in an apparently normal segment of large bowel wall.

AUTONOMIC INNERVATION OF THE HEAD

The autonomic supply to visceral structures in the head deserves special consideration (see Fig 20-4). The skin of the face and scalp (smooth muscle, glands, and vessels) receives postsynaptic sympathetic innervation only, from the superior cervical ganglion via the carotid plexus, which extends along the branches of the external carotid artery. The deeper structures (intrinsic eye muscles, salivary glands, and mucous membranes of the nose and pharynx), however, receive a dual au-



Figure 20-6. Horner's syndrome in the right eye, associated with a tumor in the superior sulcus of the right lung.

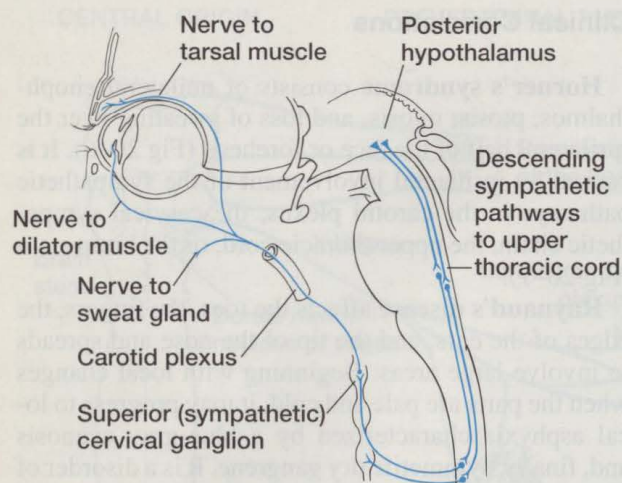


Figure 20-7. Sympathetic pathways to the eye and orbit. Interruption of these pathways inactivates the dilator muscle and thereby produces miosis, inactivates the tarsal muscle and produces the effect of enophthalmos, and reduces sweat secretion in the face (Horner's syndrome).

tonomic supply from the sympathetic and parasympathetic divisions. The supply is mediated by the internal carotid plexus (postganglionic sympathetic innervation from the superior cervical plexus) and the visceral efferent fibers in four pairs of cranial nerves (parasympathetic innervation).

There are four pairs of autonomic ganglia—ciliary, pterygopalatine, otic, and submaxillary—in the head (see Fig 20-4). Each ganglion receives a sympathetic, a parasympathetic, and a sensory root (a branch of the trigeminal nerve). Only the parasympathetic fibers make synaptic connections within these ganglia, which contain the cell bodies of the postganglionic parasympathetic fibers. The sympathetic and sensory fibers pass through these ganglia without interruption.

The **ciliary ganglion** is located between the optic nerve and the lateral rectus muscle in the posterior part of the orbit. Its parasympathetic root originates from cells in or near the Edinger-Westphal nucleus of the oculomotor nerve; its sympathetic root is composed of postganglionic fibers from the superior cervical sympathetic ganglion via the carotid plexus of the internal carotid artery. The sensory root comes from the nasociliary branch of the ophthalmic nerve. Distribution is through 10–12 short ciliary nerves that supply the ciliary muscle of the lens and the constrictor muscle of the iris. The dilator muscle of the iris is supplied by sympathetic nerves.

The **sphenopalatine (pterygopalatine) ganglion**, located deep in the pterygopalatine fossa, is associated with the maxillary nerve. Its parasympathetic root arises from cells of the superior salivatory nucleus via the glossopalatine nerve and the great petrosal nerve. The ganglion's sympathetic root comes from the internal carotid plexus by way of the deep

petrosal nerve, which joins the great superficial petrosal nerve to form the vidian nerve in the pterygoid (vidian) canal. Most of the sensory root fibers originate in the maxillary nerve, but a few arise in cranial nerves VII and IX via the tympanic plexus and vidian nerve. Distribution is through the **pharyngeal rami** to the mucous membranes of the roof of the pharynx; via the **nasal** and **palatine rami** to the mucous membranes of the nasal cavity, uvula, palatine tonsil, and hard and soft palates; and by way of the **orbital rami** to the periosteum of the orbit and the lacrimal glands.

The **otic ganglion** is located medial to the mandibular nerve just below the foramen ovale in the infratemporal fossa. Its parasympathetic root fibers arise in the inferior salivatory nucleus in the medulla and course via cranial nerve IX, the tympanic plexus, and the lesser superficial petrosal nerve; the sympathetic root comes from the superior cervical sympathetic ganglion via the plexus on the middle meningeal artery. Its sensory root probably includes fibers from cranial nerve IX and from the geniculate ganglion of cranial nerve VII via the tympanic plexus and the lesser superficial petrosal nerve. The otic ganglion supplies secretory and sensory fibers to the **parotid gland**. A few somatic motor fibers from the trigeminal nerve pass through the otic ganglion and supply the **tensor tympani** and **tensor veli palatini** muscles.

The **submaxillary ganglion** is located on the medial side of the mandible between the lingual nerve and the submaxillary duct. Its parasympathetic root fibers arise from the superior salivatory nucleus of nerve VII via the glossopalatine, chorda tympani, and lingual nerves, its sympathetic root from the plexus of the external maxillary artery, and its sensory root from the geniculate ganglion via the glossopalatine, chorda tympani, and lingual nerves. It is distributed to the **submaxillary** and **sublingual glands**.

Table 20-1. Pain innervation of the viscera.

Division	Nerve(s) or segment(s)	Structures
Parasympathetic	Vagus	Esophagus, larynx, trachea
Sympathetic	Splanchnic (T7–L1)	Stomach, spleen, small viscera, colon, kidney, ureter, bladder, (upper part), uterus (fundus), ovaries, lungs
	Somatic (C7–L1)	Parietal pleura, diaphragm, parietal peritoneum
Parasympathetic	Pelvic (S2–S4)	Rectum, trigone of the bladder, prostate, urethra, cervix of the uterus, upper vagina

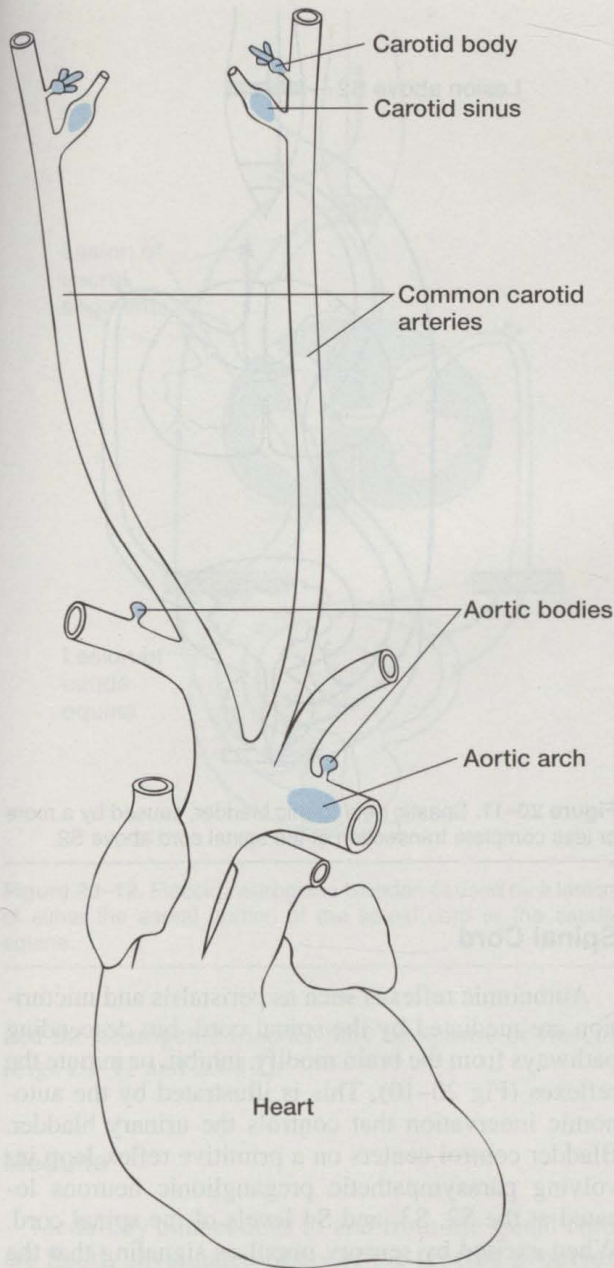


Figure 20-8. Location of carotid and aortic bodies. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.)

VISCERAL AFFERENT PATHWAYS

Visceral afferent fibers have their cell bodies in **sensory ganglia** of some of the cranial and spinal nerves. Although a few of these fibers are myelinated, most are unmyelinated and have slow conduction velocities. The pain innervation of the viscera is summarized in Table 20-1.

Pathways to the Spinal Cord

Visceral afferent fibers to the spinal cord enter by way of the **middle sacral, thoracic, and upper lum-**

bar nerves. The sacral nerves carry sensory stimuli from the pelvic organs, and the nerve fibers are involved in reflexes of the sacral parasympathetic outflow that control various sexual responses, micturition, and defecation. Axons carrying visceral pain impulses from the heart, upper digestive tract, kidney, and gall bladder travel with the thoracic and upper lumbar nerves. These visceral afferent pathways are associated with sensations such as hunger, nausea, and poorly localized, dull visceral pain (Table 20-1). Pain impulses from a viscus may converge with pain impulses arising in a particular region of the skin causing referred pain. Typical examples of the phenomenon are the shoulder pains associated with gallstone attacks and the pains of the left arm or throat associated with myocardial ischemia (see also Chapter 14).

Pathways to the Brain Stem

Visceral afferent axons in the **glossopharyngeal nerve** and (especially) the **vagus nerve** carry a variety of sensations to the brain stem from the heart, great vessels, and respiratory and gastrointestinal tracts. The ganglia involved are the inferior glossopharyngeal nerve ganglion and the inferior vagus nerve ganglion (formerly called the nodose ganglion). The afferent fibers are also involved in reflexes that regulate blood pressure, respiratory rate and depth, and heart rate through specialized receptors or receptor areas. These **baroreceptors**, which are stimulated by pressure, are located in the aortic arch and carotid sinus (Fig 20-8). Chemoreceptors that are sensitive to hypoxia are located in the aorta and carotid bodies. A chemosensitive area is located

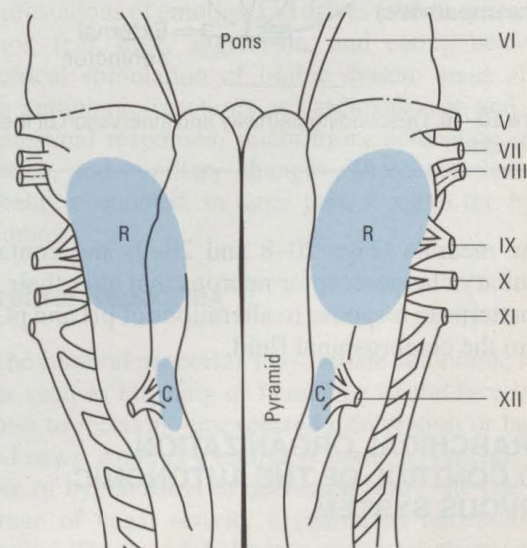


Figure 20-9. Chemosensitive areas in rostral (R) and caudal (C) parts of the ventral surface of the medulla. (Modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.)

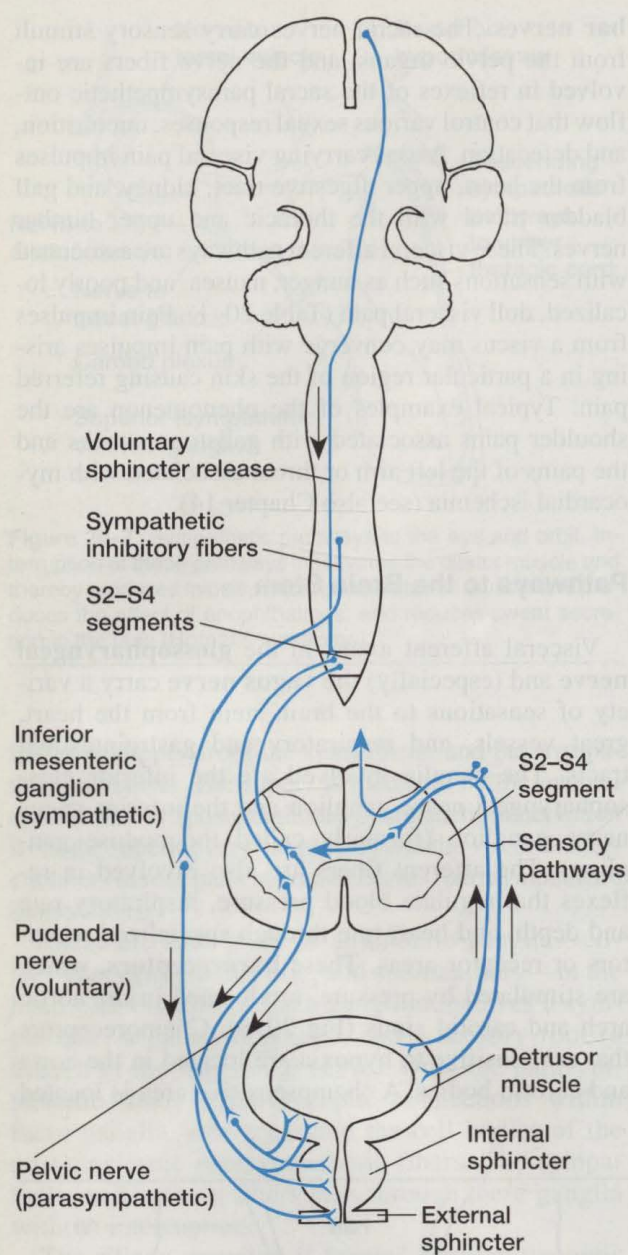


Figure 20-10. Descending pathway and innervation of the urinary bladder.

in the medulla (Figs 20-8 and 20-9) and contains medullary chemoreceptor neurons that alter their firing patterns in response to alterations of pH and $p\text{CO}_2$ within the cerebrospinal fluid.

HIERARCHICAL ORGANIZATION AND CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

There is a functional hierarchy in certain regions of the brain and spinal cord; through a complex interplay of connections, this hierarchy exerts its influence on visceral reflexes.

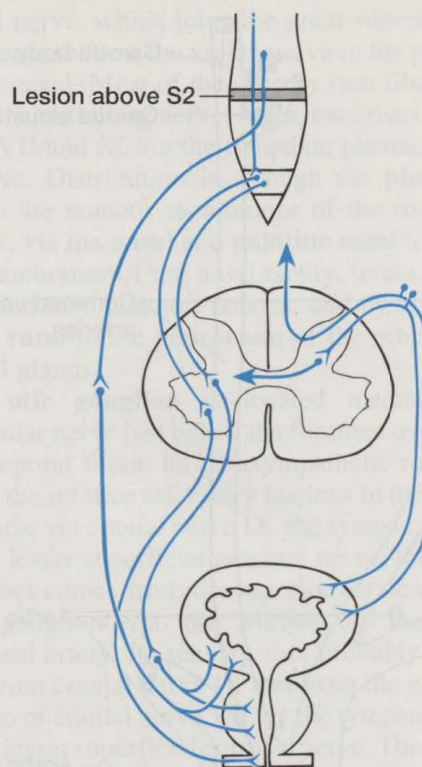


Figure 20-11. Spastic neurogenic bladder, caused by a more or less complete transection of the spinal cord above S2.

Spinal Cord

Autonomic reflexes such as peristalsis and micturition are mediated by the spinal cord, but descending pathways from the brain modify, inhibit, or initiate the reflexes (Fig 20-10). This is illustrated by the autonomic innervation that controls the urinary bladder. Bladder control centers on a primitive reflex loop involving parasympathetic preganglionic neurons located at the S2, S3, and S4 levels of the spinal cord. When excited by sensory impulses signaling that the bladder is dilated, these parasympathetic neurons send impulses that excite the detrusor muscle and inhibit the urinary sphincters, thus emptying the bladder in a reflex manner. This primitive detrusor reflex accounts for urinary function in infants. After early childhood this reflex is modulated by descending influences, including voluntary sphincter release (which begins urination) and suppression (which retards urination).

Control of urination may be impaired in patients who have suffered a transection of the spinal cord. A state of spinal shock develops, with hypotension and loss of reflexes governing micturition and defecation. Although the reflexes return after a few days or weeks, they may be incomplete or abnormal. For example, often the bladder cannot be completely emptied, which may result in cystitis, and voluntary initiation of micturition may be absent (**autonomic or neurogenic bladder**). Depending on the level of the transection, the detrusor reflex may be hyperactive or diminished,

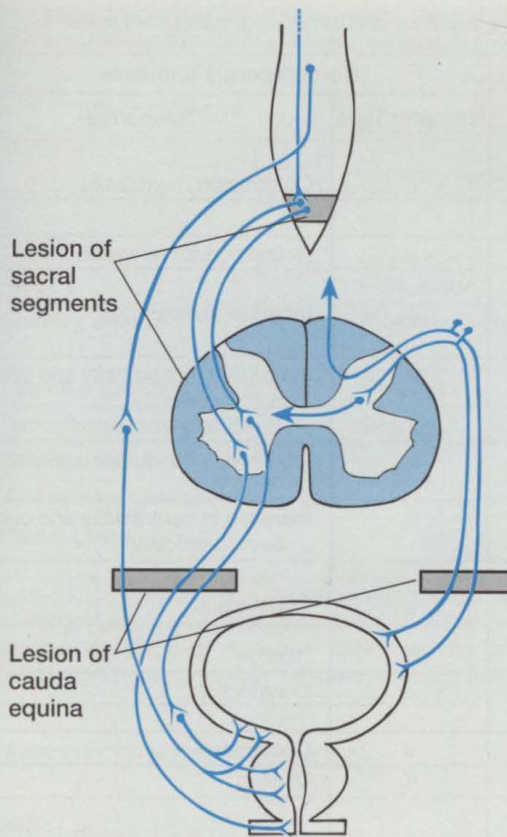


Figure 20-12. Flaccid neurogenic bladder, caused by a lesion of either the sacral portion of the spinal cord or the cauda equina.

and the neurogenic bladder may be spastic or flaccid (Figs 20-11 and 20-12).

Medulla

Medullary connections to and from the spinal cord are lightly myelinated fibers of the **tractus proprius** around the gray matter of the cord. Visceral afferent fibers of the glossopharyngeal and vagus nerves terminate in the solitary tract nucleus and are involved in control of respiratory, cardiovascular, and alimentary functions (see also Chapters 7 and 8). The major reflex actions have connections with visceral efferent nuclei of the medulla and areas of the reticular formation. These areas may contribute to the regulation of blood glucose levels and to other reflex functions, including salivation, micturition, vomiting, sneezing, coughing, and gagging. The medulla is therefore an important link in the hierarchic chain of autonomic function control.

Pons

The **nucleus parabrachialis** consists of a group of neurons that are located near the superior cerebellar pe-

duncle and that modulate the medullary neurons responsible for rhythmic respiration. This **pneumotaxic center** continues to control periodic respiration if the brain stem is transected between the pons and the medulla.

Midbrain

Accommodation, pupillary reactions to light, and other reflexes are integrated in the midbrain, near the nuclear complex of nerve III. Pathways from the hypothalamus to the visceral efferent nuclei in the brain stem course through the dorsal longitudinal fasciculus in the periaqueductal and periventricular gray matter.

Hypothalamus

A very important area of autonomic coordination, the hypothalamus integrates autonomic activities in response to changes in the internal and external environments (thermoregulatory mechanisms; see also Chapter 9). The posterior portion of the hypothalamus is involved with sympathetic function, and the anterior portion is involved with parasympathetic function. The most important descending pathway is the dorsal longitudinal fasciculus, and the connections with the hypophysis aid in the influence of the hypothalamus on visceral functions.

Limbic System

The limbic system has been called the visceral brain and has close anatomic and functional links with the hypothalamus (see also Chapter 19). Various portions of the limbic system exert control over the visceral manifestations of emotion and drives such as sexual behavior, fear, rage, aggression, and eating behavior. Electrical stimulation of limbic system areas elicits such autonomic reactions as cardiovascular and gastrointestinal responses, micturition, defecation, piloerection, and pupillary changes. These reactions are probably channeled, in large part, through the hypothalamus.

Cerebral Neocortex

The cerebral neocortex may initiate autonomic reactions such as blushing or blanching of the face in response to receiving unexpected information or bad or good news. Another example is fainting (syncope) because of hypotension or decreased heart rate due to a barrage of vagal activity triggered by an emotional stimulus. These widely known anecdotal observations are confirmed by the findings that destruction or stimulation of neocortical areas in humans can interfere with the normal regulation of many autonomic responses.

Table 20–2. Responses of effector organs to autonomic nerve impulses and circulating catecholamines.

Effector Organs	Cholinergic Response	Noradrenergic Impulses	
		Receptor Type	Response
Eye			
Radial muscle of iris	...	α	Contraction (mydriasis)
Sphincter muscle of iris	Contraction (miosis)	...	...
Ciliary muscle	Contraction for near vision	β	Relaxation for far vision
Heart			
S-A node	Decrease in heart rate; vagal arrest	β_1	Increase in heart rate
Atria	Decrease in contractility and (usually) increase in conduction velocity	β_1	Increase in contractility and conduction velocity
A-V node and conduction system	Decrease in conduction velocity; A-V block	β_1	Increase in conduction velocity
Ventricles	...	β_2	Increase in contractility and conduction velocity
Arterioles			
Coronary, skeletal muscle, pulmonary, abdominal viscera, renal	Dilation	α	Constriction
		β_2	Dilation
Skin and mucosa, cerebral, salivary glands	...	α	Constriction
Systemic veins	...	α	Constriction
		β_2	Dilation
Lung			
Bronchial muscle	Contraction	β_2	Relaxation
Bronchial glands	Stimulation	?	Inhibition(?)
Stomach			
Motility and tone	Increase	α, β_2	Decrease (usually)
Sphincters	Relaxation (usually)	α	Contraction (usually)
Secretion	Stimulation	...	Inhibition(?)
Intestine			
Motility and tone	Increase	α, β_2	Decrease
Sphincters	Relaxation (usually)	α	Contraction (usually)
Secretion	Stimulation	...	Inhibition(?)
Gallbladder and ducts	Contraction	...	Relaxation
Urinary bladder			
Detrusor	Contraction	β	Relaxation (usually)
Trigon and sphincter	Relaxation	α	Contraction
Ureter			
Motility and tone	Increase(?)	α	Increase (usually)
Uterus	Variable*	α, β_2	Variable†
Male sex organs	Erection	α	Ejaculation
Skin			
Pilomotor muscles	...	α	Contraction
Sweat glands	Generalized secretion	α	Slight localized secretion†
Spleen capsule	...	α	Contraction
		β_2	Relaxation
Adrenal medulla	Secretion of epinephrine and norepinephrine	...	...
Liver	...	α, β_2	Glycogenolysis

(continued)

Table 20–2 (cont'd). Responses of effector organs to autonomic nerve impulses and circulating catecholamines.

Effector Organs	Cholinergic Response	Noradrenergic Impulses	
		Receptor Type	Response
Pancreas Acini	Increase secretion	α	Decreased secretion
Islets	Increased insulin and glucagon secretion	α	Decreased insulin and glucagon secretion
		β_2	Increased insulin and glucagon secretion
Salivary glands	Profuse watery secretion	α	Thick secretion
		β_2	Amylase secretion
Lacrimal glands	Secretion	...	...
Nasopharyngeal glands	Secretion	...	...
Adipose tissue	...	β_1	Lipolysis
Juxtaglomerular cells	...	β_1	Increased renin secretion
Pineal gland	...	β	Increased melatonin synthesis and secretion

Modified from Gilman AG et al (editors): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. Macmillan, 1990. Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.

*Depends on stage of menstrual cycle, amount of circulating estrogen and progesterone, pregnancy, and other factors.

†On palms of hands and in some other locations (adrenergic sweating).

TRANSMITTER SUBSTANCES

Types

Autonomic neurotransmitters mediate all visceral functions; the principal transmitter agents are acetylcholine and norepinephrine (see also Chapter 3). The two divisions of the autonomic system (parasympathetic and sympathetic) tend to release different transmitters (acetylcholine and norepinephrine) from their postganglionic neurons (although there are several exceptions, as noted in a later section), providing a pharmacologic basis for their opposing actions.

Acetylcholine is liberated at all preganglionic endings. Acetylcholine is also released by parasympathetic postganglionic neurons and by sympathetic postganglionic neurons that project to sweat glands or mediate vasodilation. High concentrations of acetylcholine, choline acetyltransferase, and acetylcholinesterase are found in cholinergic nerve endings.

Norepinephrine (levarterenol), a catecholamine, is the chemical transmitter at most sympathetic postganglionic endings. Norepinephrine and its methyl derivative, **epinephrine**, are secreted by the adrenal medulla. Although many viscera contain both norepinephrine and epinephrine, the latter is not considered to be a mediator at sympathetic endings; only the norepinephrine content can be related to the number of sympathetic nerve endings in the organ. Drugs that block the effects of epinephrine but not norepinephrine have little effect on the response of most organs to stimulation of their adrenergic nerve supply.

Substance P, somatostatin, vasoactive intestinal peptide (VIP), adenosine, and adenosine triphosphate (ATP) may also function as visceral neurotransmitters.

Functions

The autonomic nervous system can be divided into **cholinergic** and **adrenergic** divisions, based on the chemical mediator released. Cholinergic neurons include preganglionic and parasympathetic postganglionic neurons, sympathetic postganglionic neurons to sweat glands, and sympathetic vasodilator neurons to blood vessels in skeletal muscle. There is usually no acetylcholine in circulating blood, and the effects of localized cholinergic discharge are generally discrete and short-lived because of high concentrations of cholinesterase at the cholinergic nerve endings (Fig 20–13; Table 20–2).

In the adrenal medulla, the postganglionic cells have lost their axons and become specialized for secreting catecholamine (epinephrine) directly into the blood; the cholinergic preganglionic neurons to these cells act as the secretomotor nerve supply to the adrenal gland. Sympathetic postganglionic neurons are generally considered adrenergic except for the sympathetic vasodilator neurons and sweat gland neurons. Notice that norepinephrine has a more prolonged and wider action than does acetylcholine (Fig 20–14).

Receptors

The target tissues on which norepinephrine acts can be separated into two categories, based on their different sensitivities to certain drugs. This is related to the existence of two types of catecholamine receptors— α and β —in the target tissues. The α **receptors** mediate vasoconstriction, and the β **receptors** mediate such actions as the increase in cardiac rate and the strength of

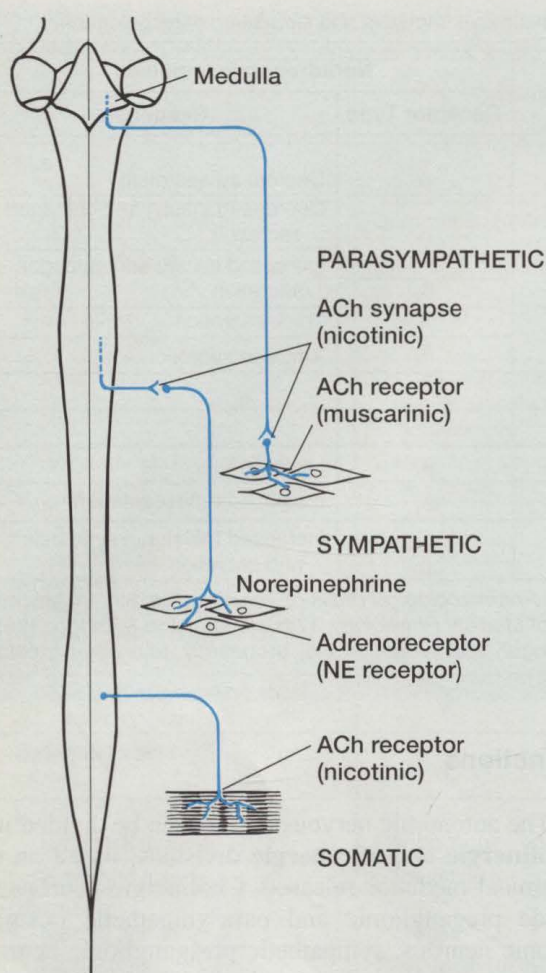


Figure 20-13. Schematic diagram showing some anatomic and pharmacologic features of autonomic and somatic motor nerves.

cardiac contraction. There are two subtypes of α receptors (α_1 and α_2) and two subtypes of β receptors (β_1 and β_2). The α and β receptors occur in both preganglionic endings and postganglionic membranes. The preganglionic β -adrenergic receptors are of the β_1 type; the postganglionic receptors are of the β_2 type (Fig 20-15 and Table 20-2).

Effects of Drugs on the Autonomic Nervous System

Certain drugs affect the autonomic nervous system by mimicking or blocking cholinergic or adrenergic discharges (Table 20-3). Drugs can also alter other activities such as synthesis, storage in nerve endings, release near effector cells, action on effector cells, and termination of transmitter activity. Sometimes, a drug may affect two transmitter systems rather than one.

Despite apparent similarities in the transmitter chemistry of preganglionic and postganglionic cholinergic neurons, agents can act differently at these

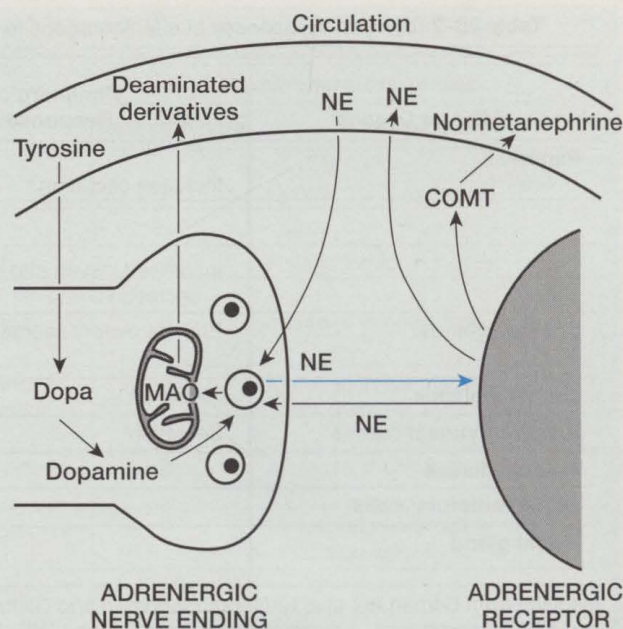


Figure 20-14. Formation, uptake, and metabolism of norepinephrine at adrenergic nerve endings. Norepinephrine in the granulated vesicles is released from the endings mainly by action potentials in the sympathetic nerves. Some of the norepinephrine constantly diffuses from the granules to the mitochondria, however, where it is oxidized to deaminated derivatives. Norepinephrine in the vesicles is formed from dopamine, taken up from the circulation, and taken up again after its release from the endings (reuptake). NE, norepinephrine; COMT, catechol-O-methyltransferase; MAO, monamine oxidase. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.)

sites. **Muscarine** has little effect on autonomic ganglia, for example, but acts on smooth muscle and glands, where it mimics the effects of acetylcholine. The acetylcholine receptors on these cells are termed **muscarinic**. Drugs with muscarinic action include acetylcholine, acetylcholine-related substances, and inhib-

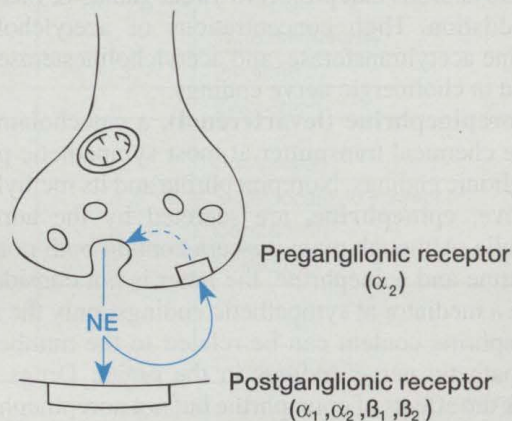


Figure 20-15. Preganglionic and postganglionic receptors at the ending of a noradrenergic neuron. The preganglionic receptor shown is α ; the postganglionic receptors can be α_1 , α_2 , β_1 , or β_2 . (Reproduced, with permission, from Ganong, WF: *Review of Medical Physiology*, 17th ed. Appleton & Lange, 1995.)

Table 20-3. Some chemical agents that affect sympathetic activity, listing only the principal actions of the agents.

Site of Action	Agents That Augment Sympathetic Activity	Agents That Depress Sympathetic Activity
Sympathetic ganglia	Stimulate postganglionic neurons Nicotine Dimethphenylpiperazinium Inhibit acetylcholinesterase Physostigmine (eserine) Neostigmine (Prostigmin) Parathion	Block conduction Chlorisondamine* Hexamethonium* Mecamylamine (Inversine) Pentolinium* Tetraethylammonium* Trimethaphan (Arfonad) Acetylcholine and anticholinesterase drugs in high concentrations
Endings of postganglionic neurons	Release norepinephrine Tyramine Ephedrine Amphetamine	Block norepinephrine synthesis Metyrosine Interfere with norepinephrine storage Reserpine Guanethidine (Ismelin) [†] Prevent norepinephrine release Bretylium tosylate Guanethidine (Ismelin) [†] Form false transmitters Methyl dopa (Aldomet)
α Receptors	Stimulate α_1 receptors Methoxamine (Vasoxyl) Phenylephrine (Neo-Synephrine) Stimulate α_2 receptors Clonidines [‡]	Block α receptors Phenoxybenzamine (Dibenzylamine) Phentolamine (Regitine) Prazosin (blocks α_1) Yohimbine (blocks α_2)
β Receptors	Stimulate β receptors Isoproterenol (Isuprel)	Block β receptors Propranolol (Inderal) and others (block β_1 and β_2) Metoprolol and others (block β_1) Butoxamine [†] (blocks β_2)

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*Not available in the USA.

[†]Note that guanethidine is believed to have 2 principal actions.

[‡]Clonidine stimulates α_2 receptors in the periphery, but along with others α_2 agonists that cross the blood-brain barrier, it also stimulates α_2 receptors in the brain which decrease sympathetic output. Therefore, the overall effect is decreased sympathetic discharge.

itors of cholinesterase (certain nerve gases, etc). Atropine, belladonna, and other natural and synthetic belladonna-like drugs block the muscarine effects of acetylcholine by preventing the mediator from acting on visceral effector organs.

Some actions of acetylcholine, including the transmission of impulses from pre- to postganglionic neurons, are not affected by atropine. Because nicotine produces the same actions, the actions of acetylcholine in the presence of atropine are called its nicotine effects, and the receptors are called **nicotinic** acetylcholine receptors. Nicotinic acetylcholine receptors are present at neuromuscular junctions and at the synapses between preganglionic and postganglionic neurons.

Curariform agents, hexamethonium, and mecamlamine act principally by blocking transmission at the cholinergic motor neuron endings on skeletal muscle fibers; they were used in the past in the treatment of hypertension.

Drugs that block the effects of norepinephrine on visceral effectors are often called adrenergic-neuron-blocking agents, adrenolytic agents, or sympatholytic agents.

Sensitization

Autonomic effectors (smooth muscle, cardiac muscle, and glands) that are partially or completely separated from their normal nerve connections become more sensitive to the action of the neurotransmitters that normally impinge on them; this has been termed **denervation hypersensitivity**. Known as Cannon's law of denervation, the effect is more pronounced after postganglionic interruption than after preganglionic interruption.

CASE 26

A 55-year-old male clerk consulted his physician about drooling, difficulty in swallowing, and a "funny-sounding" voice. Indirect laryngoscopy showed decreased motility of the right vocal cord. Findings in all other examinations and tests were within normal limits. Drugs were given to control the patient's hypersalivation.

Eight months later, the patient returned with a 10-day history of lightheadedness and fainting. He was referred to a hospital for observation and examination. The only additional abnormal findings were fasciculations in the right side of the tongue and changes in blood pressure with postural changes (lying down, 140/90; sitting up, 100/70; and standing up, too low to read). Lumbar puncture analysis showed a protein level of 95 mg/dL. While in the hospital, the patient had one episode of rotatory vertigo. After four days, he went back to work.

Three months later, the patient returned with complaints of dizziness, fainting, and increased problems in swallowing; his speech was difficult to understand. His drop in blood pressure with postural changes was

still present. Neurologic examination showed a normal mental status; flat optic discs; visual fields full, with pupils normal and reactive to light; normal extraocular movements; bilateral neural hearing deficits; dysarthria; midline palate location with normal gag reflex; and a weak tongue that deviated to the right when protruded. The patient's gait was wide-based and unsteady. The heel-to-shin test showed ataxia on the right and other cerebellar tests results were normal. The deep tendon reflexes were also normal. A CT scan showed moderate ventricular enlargement.

Where is the lesion? What is the nature of the lesion? What is the explanation for the autonomic dysfunctions?

Cases are discussed further in Chapter 26.

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